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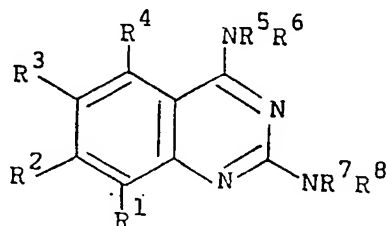
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Date of publication of the amended claims:

13 July 1989 (13.07.89)

(54) Title: COMPOUNDS



(I)

(57) Abstract

Compounds of structure (I) in which R<sup>1</sup> to R<sup>4</sup> are the same or different and are each hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, phenyl, C<sub>1-4</sub>alkylthio, C<sub>1-4</sub>alkanoyl, amino, C<sub>1-6</sub>alkylamino, diC<sub>1-4</sub>alkylamino, halogen or trifluoromethyl provided that at least two of R<sup>1</sup> to R<sup>4</sup> are hydrogen. R<sup>5</sup> and R<sup>6</sup> are the same, or different and are each hydrogen, C<sub>1-4</sub>alkyl, -(CH<sub>2</sub>)<sub>n</sub>Ar in which n is 0 to 4 and Ar is an optionally substituted phenyl group, or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring; and R<sup>7</sup> and R<sup>8</sup> are the same or different and are each hydrogen, C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>n</sub>Ar<sup>1</sup> in which n is 0 to 4 and Ar<sup>1</sup> is an optionally substituted phenyl group, or R<sup>7</sup> and R<sup>8</sup> together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring; and pharmaceutically acceptable salts thereof, processes for their preparation, pharmaceutical compositions containing them and their use in therapy as inhibitors of gastric acid secretion.

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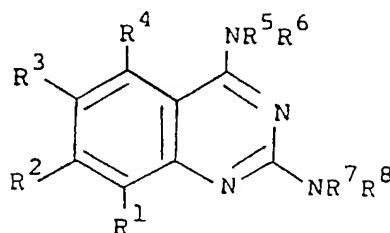
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## AMENDED CLAIMS

[received by the International Bureau on 16 June 1989 (16.06.89):  
original claims 1 and 10 amended; new claim 12 added; other claims unchanged (6 pages)]

1. A compound of structure (I)



(I)

in which

$R^1$  to  $R^4$  are the same or different and are each hydrogen,  
 $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, phenyl,  $C_{1-4}$  alkylthio,  
 $C_{1-4}$  alkanoyl, amino,  $C_{1-6}$  alkylamino, di $C_{1-4}$  alkylamino,  
halogen or trifluoromethyl provided that at least two  
of  $R^1$  to  $R^4$  are hydrogen.

$R^5$  and  $R^6$  are the same, or different and are each hydrogen,  
 $C_{1-4}$  alkyl,  $-(CH_2)_n Ar$  in which  $n$  is 0 to 4 and  $Ar$  is an  
optionally substituted phenyl group or  $R^5$  and  $R^6$   
together with the nitrogen atom to which they are  
attached form a saturated or unsaturated carbocyclic  
ring; and:

$R^7$  and  $R^8$  are the same or different and are each hydrogen,  
 $C_{1-4}$  alkyl,  $(CH_2)_n Ar^1$  in which  $n$  is 0 to 4 and  $Ar^1$  is  
an optionally substituted phenyl group, or  $R^7$  and  $R^8$   
together with the nitrogen atom to which they are  
attached form a saturated or unsaturated carbocyclic  
ring;

or a pharmaceutically acceptable salt thereof, provided that

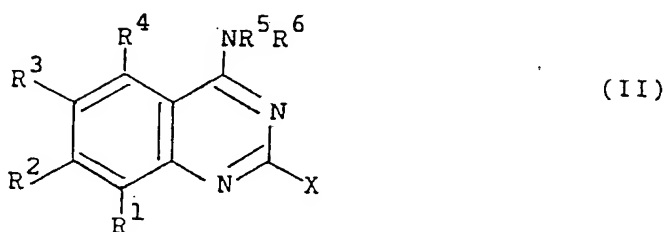
- ° R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> are not, at the same time, all hydrogen;
- 5 ° at least one of R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup> and R<sup>8</sup> is a (CH<sub>2</sub>)<sub>n</sub>Ar or (CH<sub>2</sub>)<sub>n</sub>Ar<sup>1</sup> group as appropriate; and
- ° when R<sup>1</sup> and R<sup>4</sup> are both hydrogen and one of R<sup>2</sup> and R<sup>3</sup> is C<sub>1-4</sub>alkoxy, the other is not hydrogen or C<sub>1-4</sub>alkoxy.

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2. A compound according to claim 1 in which  $R^2$  to  $R^4$  are hydrogen and  $R^1$  is hydrogen or  $C_{1-4}$ alkoxy.
3. A compound according to claim 2 in which one of  $R^5$  and  $R^6$  is  $(CH_2)_n Ar$  in which  $n$  is 0 to 4 and  $Ar$  is an optionally substituted phenyl group and the other is  $C_{1-4}$ alkyl.
4. A compound according to claim 3 in which  $n$  is 0.
5. A compound according to claim 4 in which one of  $R^7$  and  $R^8$  is hydrogen and the other is  $-(CH_2)_n Ar^1$  in which  $n$  is 0 to 4 and  $Ar^1$  is an optionally substituted phenyl ring.
6. A compound according to claim 1 which is  
2-amino-8-methoxy-4-(2-methylphenylamino)quinazoline  
2,4-Bis-(N-methylphenylamino)quinazoline  
4-(N-methylphenylamino)-2-(2-methylphenylamino)-8-methoxy-  
quinazoline  
2-(2-methylphenylamino)-4-(N-methylphenylamino)quinazoline  
2-phenylamino-4-(N-methylphenylamino)quinazoline  
2-[(2-methyl-4-fluorophenyl)amino]-4-(N-methylphenylamino)-  
quinazoline  
2-(2-methylphenylamino)-4-phenylaminoquinazoline  
or a pharmaceutically acceptable salt thereof.
7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 and a pharmaceutical carrier.
8. A compound according to any one of claims 1 to 6 for use as a therapeutic agent.

9. A process for the preparation of a compound according to claim 1 which comprises :

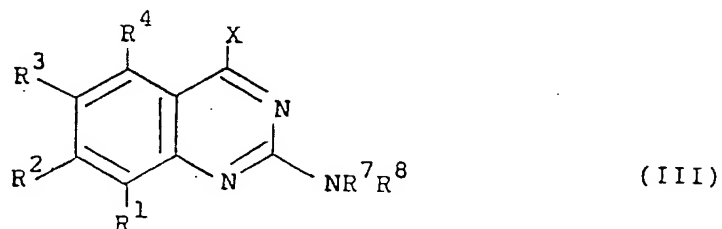
(a) reaction of a compound of structure (II)



in which  $R^1$  to  $R^6$  are as described for structure (I) except that where necessary they are in protected form, and X is a group displaceable by an amine, with an amine of structure  $R^7R^8NH$  in which  $R^7$  and  $R^8$  are as described for structure (I); or

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(b) reaction of a compound of structure (III)

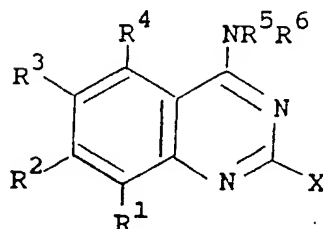


in which  $R^1$  to  $R^4$  and  $R^7$  and  $R^8$  are as described for structure (I) and X is a group displaceable by an amine, with an amine of structure  $R^5R^6NH$  in which  $R^5$  and  $R^6$  are as described for structure (I); and optionally thereafter,

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- removing any protecting groups;
  - forming a pharmaceutically acceptable salt.
- 35

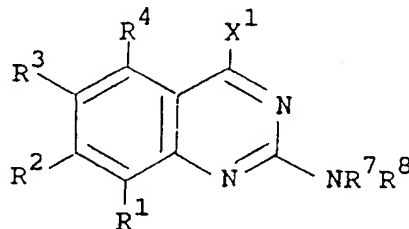
10. A compound of structure (IIA)



(IIA)

in which  $R^1$  to  $R^4$  are as described for structure (I) in claim 1,  $R^5$  is hydrogen or  $C_{1-4}$ alkyl and  $R^6$  is  $(CH_2)_nAr$ , in which  $n$  is 0 to 4 and  $Ar$  is an optionally substituted phenyl group and  $X$  is a group displaceable by an amine.

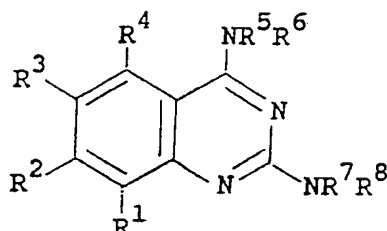
11. A compound of structure (IIIA)



(IIIA)

in which  $R^1$  to  $R^4$  are as described for structure (I) in claim 1,  $R^7$  is hydrogen or  $C_{1-4}$ alkyl and  $R^8$  is  $(CH_2)_nAr^1$  in which  $n$  is 0 to 4 and  $Ar^1$  is an optionally substituted phenyl group and  $X$  is a group displaceable by an amine.

12. The use of a compound of formula (IA)



(IA)

in which

R<sup>1</sup> to R<sup>4</sup> are the same or different and are each hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, phenyl, C<sub>1-4</sub>alkylthio, C<sub>1-4</sub>alkanoyl, amino, C<sub>1-6</sub>alkylamino, diC<sub>1-4</sub>alkylamino, halogen or trifluoromethyl provided that at least two of R<sup>1</sup> to R<sup>4</sup> are hydrogen.

R<sup>5</sup> and R<sup>6</sup> are the same, or different and are each hydrogen, C<sub>1-4</sub>alkyl, -(CH<sub>2</sub>)<sub>n</sub>Ar in which n is 0 to 4 and Ar is an optionally substituted phenyl group or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring; and;

R<sup>7</sup> and R<sup>8</sup> are the same or different and are each hydrogen, C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>n</sub>Ar<sup>1</sup> in which n is 0 to 4 and Ar<sup>1</sup> is an optionally substituted phenyl group, or R<sup>7</sup> and R<sup>8</sup> together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring;

or a pharmaceutically acceptable salt thereof,

for the manufacture of a medicament for the treatment of gastrointestinal diseases.

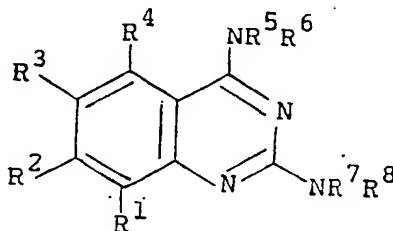




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<p>(71) Applicant: SMITHKLINE BECKMAN INTERC-</p>		<p><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
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(54) Title: COMPOUNDS



(I)

**(57) Abstract**

Compounds of structure (I) in which R<sup>1</sup> to R<sup>4</sup> are the same or different and are each hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, phenyl, C<sub>1-4</sub>alkylthio, C<sub>1-4</sub>alkanoyl, amino, C<sub>1-6</sub>alkylamino, diC<sub>1-4</sub>alkylamino, halogen or trifluoromethyl provided that at least two of R<sup>1</sup> to R<sup>4</sup> are hydrogen. R<sup>5</sup> and R<sup>6</sup> are the same, or different and are each hydrogen, C<sub>1-4</sub>alkyl, -(CH<sub>2</sub>)<sub>n</sub>Ar in which n is 0 to 4 and Ar is an optionally substituted phenyl group, or R<sup>5</sup> and R<sup>6</sup> together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring; and R<sup>7</sup> and R<sup>8</sup> are the same or different and are each hydrogen, C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>n</sub>Ar<sup>1</sup> in which n is 0 to 4 and Ar<sup>1</sup> is an optionally substituted phenyl group, or R<sup>7</sup> and R<sup>8</sup> together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring; and pharmaceutically acceptable salts thereof, processes for their preparation, pharmaceutical compositions containing them and their use in therapy as inhibitors of gastric acid secretion.

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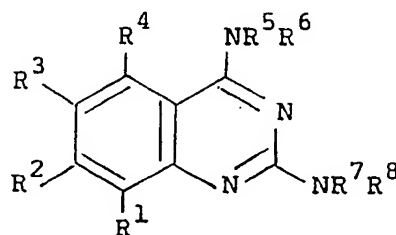
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Compounds

The present invention relates to substituted  
quinazoline derivatives, processes for their preparation,  
5 intermediates useful in their preparation, pharmaceutical  
compositions containing them and their use in therapy.

Accordingly the present invention provides, in a  
first aspect compounds of structure (I)

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(I)

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in which

$R^1$  to  $R^4$  are the same or different and are each hydrogen,  
20  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, phenyl,  $C_{1-4}$ alkylthio,  
 $C_{1-4}$ alkanoyl, amino,  $C_{1-6}$ alkylamino,  $diC_{1-4}$ alkylamino,  
halogen or trifluoromethyl provided that at least two  
of  $R^1$  to  $R^4$  are hydrogen.

25  $R^5$  and  $R^6$  are the same, or different and are each hydrogen,  
 $C_{1-4}$ alkyl,  $-(CH_2)_nAr$  in which n is 0 to 4 and Ar is  
an optionally substituted phenyl group, or  $R^5$  and  $R^6$   
together with the nitrogen atom to which they are  
attached form a saturated or unsaturated carbocyclic  
30 ring; and;

$R^7$  and  $R^8$  are the same or different and are each hydrogen,  
 $C_{1-4}$ alkyl,  $(CH_2)_nAr^1$  in which n is 0 to 4 and  $Ar^1$  is  
an optionally substituted phenyl group, or  $R^7$  and  $R^8$   
35 together with the nitrogen atom to which they are  
attached form a saturated or unsaturated carbocyclic  
ring;

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and pharmaceutically acceptable salts thereof.

Suitably at least two of  $R^1$  to  $R^4$  are hydrogen and the others are the same or different and are each hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, phenyl,  $C_{1-4}$ alkylthio,  $C_{1-4}$ alkanoyl, amino,  $C_{1-4}$ alkylamino, di $C_{1-4}$ alkylamino, halogen, trifluoromethyl or nitro. More suitably, three of  $R^1$  to  $R^4$  are hydrogen and the other is hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, phenyl,  $C_{1-4}$ alkylthio,  $C_{1-4}$ alkanoyl, amino,  $C_{1-4}$ alkylamino, di $C_{1-4}$ alkylamino, halogen or trifluoromethyl; preferably  $R^2$  to  $R^4$  are hydrogen and  $R^1$  is hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy, phenyl,  $C_{1-4}$ alkylthio,  $C_{1-4}$ -alkanoyl, amino,  $C_{1-4}$ alkylamino, di $C_{1-4}$ alkylamino, halogen or trifluoromethyl; more preferably  $R^2$  to  $R^4$  are hydrogen and  $R^1$  is hydrogen,  $C_{1-4}$ alkyl or  $C_{1-4}$ alkoxy; most preferably  $R^2$  to  $R^4$  are hydrogen and  $R^1$  is hydrogen or  $C_{1-4}$ alkoxy, in particular methoxy.

Suitably  $R^5$  and  $R^6$  are the same or different and are each hydrogen or  $(CH_2)_n$ Ar in which n is 0 to 4 and Ar is an optionally substituted phenyl group or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring. More suitably, one of  $R^5$  and  $R^6$  is hydrogen or  $C_{1-4}$ alkyl and the other is hydrogen,  $C_{1-4}$ alkyl or  $(CH_2)_n$ Ar. Most suitably one of  $R^5$  and  $R^6$  is hydrogen or  $C_{1-4}$ alkyl and the other is  $(CH_2)_n$ Ar. Preferably one of  $R^5$  and  $R^6$  is  $C_{1-4}$ alkyl and the other is  $(CH_2)_n$ Ar; most preferably one of  $R^5$  and  $R^6$  is  $C_{1-4}$ alkyl, in particular methyl and the other is  $(CH_2)_n$ Ar in which n is 0.

Suitably, Ar is unsubstituted or substituted by 1 to 3 substituents selected from hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkylthio, halogen, cyano, amino, hydroxy, carbamoyl, carboxy,  $C_{1-4}$ alkanoyl or trifluoromethyl. More suitably, Ar is unsubstituted or substituted by two substituents selected from hydrogen,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,

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C<sub>1-4</sub>alkylthio, halogen, cyano, amino, hydroxy, carbamoyl, carboxy, C<sub>1-4</sub>alkanoyl or trifluoromethyl. More preferably, Ar is unsubstituted or substituted by two substituents selected from C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy. Most preferably, Ar is unsubstituted or substituted by a single substituent selected from the above-noted groups, in particular C<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkoxy.

Suitably, R<sup>7</sup> and R<sup>8</sup> are the same or different and are each hydrogen, C<sub>1-4</sub>alkyl, (CH<sub>2</sub>)<sub>n</sub>Ar<sup>1</sup> in which n is 0 to 4 and Ar<sup>1</sup> is an optionally substituted phenyl group, or R<sup>7</sup> and R<sup>8</sup> together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring. More suitably one of R<sup>7</sup> and R<sup>8</sup> is hydrogen or C<sub>1-4</sub>alkyl and the other is hydrogen, C<sub>1-4</sub>alkyl or (CH<sub>2</sub>)<sub>n</sub>Ar<sup>1</sup>, or R<sup>7</sup> and R<sup>8</sup> together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring. Most suitably, one of R<sup>7</sup> and R<sup>8</sup> is hydrogen or C<sub>1-4</sub>alkyl and the other is hydrogen, C<sub>1-4</sub>alkyl or (CH<sub>2</sub>)<sub>n</sub>Ar<sup>1</sup>. Preferably one of R<sup>7</sup> and R<sup>8</sup> is hydrogen or C<sub>1-4</sub>alkyl and the other is (CH<sub>2</sub>)<sub>n</sub>Ar<sup>1</sup>; more preferably one of R<sup>7</sup> and R<sup>8</sup> is hydrogen and the other is (CH<sub>2</sub>)<sub>n</sub>Ar<sup>1</sup>; most preferably, one of R<sup>7</sup> and R<sup>8</sup> is hydrogen and the other is (CH<sub>2</sub>)<sub>n</sub>Ar<sup>1</sup> in which n is 0.

Suitably, the group Ar<sup>1</sup> is unsubstituted or optionally substituted by 1 to 3 substituents as hereinabove described for the group Ar in R<sup>5</sup>. Preferably the group Ar<sup>1</sup> is unsubstituted or optionally substituted by two substituents as hereinabove described for Ar. Preferably the group Ar<sup>1</sup> is unsubstituted or substituted by two groups, which may be the same or different; more preferably the group Ar<sup>1</sup> is unsubstituted or substituted by two groups which may be the same or different and selected from C<sub>1-4</sub>alkyl and C<sub>1-4</sub>alkoxy. Most preferably the group Ar<sup>1</sup> is unsubstituted or substituted by one or two groups, for example a

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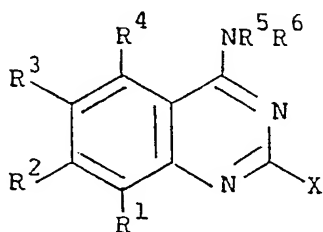
C<sub>1-4</sub> alkyl group, in particular a methyl group or a halogen atom, in particular a fluorine atom; or a C<sub>1-4</sub> alkyl group and a halogen atom in particular a methyl group and fluorine atom. Particularly preferably the group Ar<sup>1</sup> is substituted by a methyl group in the 2-position of the ring and a fluorine atom in the 4-position of the ring.

C<sub>1-4</sub> alkyl groups (either alone or as part of another group) can be straight or branched.

It will be appreciated that compounds of structure (I) in which one or more of R<sup>1</sup> to R<sup>8</sup> is a C<sub>3-4</sub> alkyl group (either alone or as part of another group) may contain an assymmetric centre due to the presence of the C<sub>3-4</sub> alkyl group. Such compounds will exist as two (or more) optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are included within the scope of the present invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention.

The compounds of the present invention can be prepared by processes analogous to those known in the art. The present invention therefore provides in a further aspect a process for the preparation of a compound of structure (I) or a pharmaceutically acceptable salt thereof which comprises

(a) reaction of a compound of structure (II)

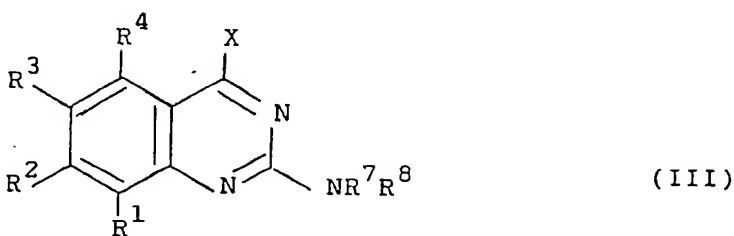


(II)

- 5 -

in which  $R^1$  to  $R^6$  are as described for structure (I) except that where necessary they are in protected form, and X is a group displaceable by an amine, with an amine of structure  $R^7R^8NH$  in which  $R^7$  and  $R^8$  are as described for structure (I); or

(b) reaction of a compound of structure (III)



15 in which  $R^1$  to  $R^4$  and  $R^7$  and  $R^8$  are as described for structure (I) and X is a group displaceable by an amine, with an amine of structure  $R^5R^6NH$  in which  $R^5$  and  $R^6$  are as described for structure (I); and optionally

20 thereafter,

- removing any protecting groups;
- forming a pharmaceutically acceptable salt.

25 Suitable groups displaceable by an amine, X, will be apparent to those skilled in the art and include, for example, halogen, in particular chlorine,  $SC_{1-4}$ alkyl, such as methylthio, hydroxy and phenoxy.

30 Reaction of a compound of structure (II) with an amine  $R^7R^8NH$  is suitably carried out in an inert solvent at elevated temperature. Preferably the reaction is carried out in the absence of a solvent in a sealed

35 receptacle at elevated temperature.

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Reaction of a compound of structure (III) with an amine  $R^5R^6NH$  is suitably carried out in the presence or absence of an inert solvent at elevated temperature. Suitable solvents include, for example  $C_{1-4}$  alkanols such as isopropanol or butanol, preferably isopropanol.

In particular, leaving groups  $X$  and  $X^1$  are halogen, preferably chlorine, and can be displaced by appropriate amines  $R^5R^6NH$  and  $R^7R^8NH$  under the general conditions described above and in the specific examples. Other conditions and reagents depending on the nature of the leaving groups will be apparent to those skilled in the art; for example compounds of structure (I) in which  $R^5$  and  $R^6$  are both hydrogen, can be prepared from the corresponding compounds of structure (III) in which  $X$  is hydroxy by reaction with phenylphosphordiamidate using the method described in J. Het. Chem (1972), 9, 1235.

Pharmaceutically acceptable acid addition salts of the compounds of structure (I) can be prepared by standard procedures by, for example, reaction with suitable organic and inorganic acids the nature of which will be apparent to persons skilled in the art. For example, pharmaceutically acceptable salts can be formed by reaction with hydrochloric, sulphuric, or phosphoric acids; aliphatic, aromatic or heterocyclic sulphonic acids or carboxylic acids such as, for example, citric, maleic or fumaric acids.

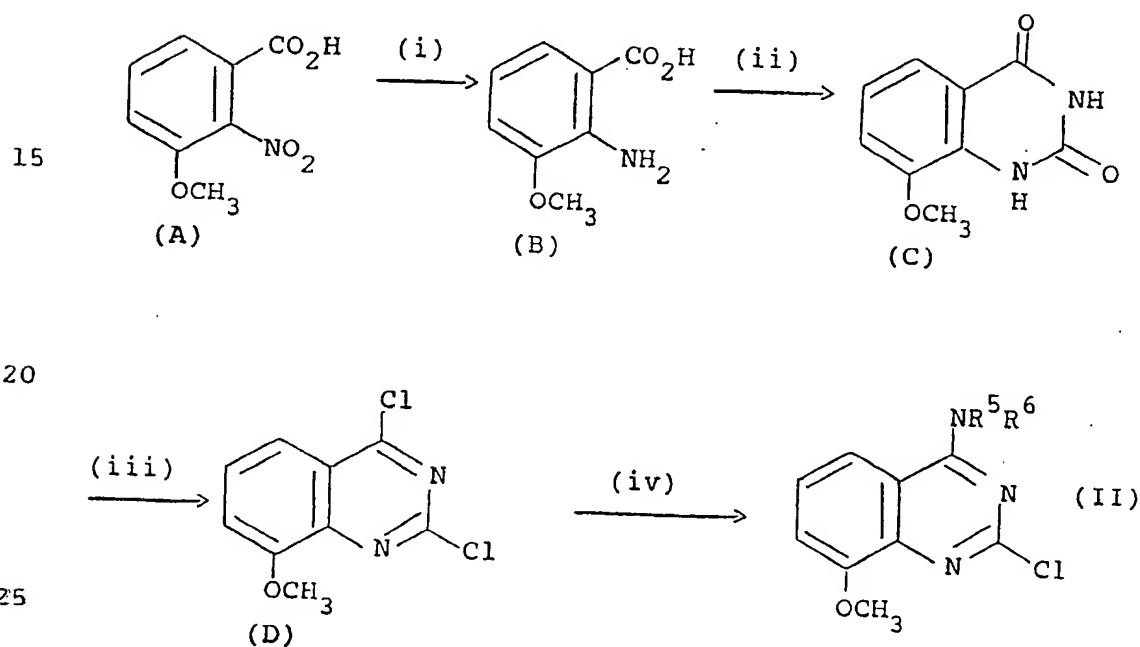
The intermediate compounds of structure (II) and (III) can be prepared by procedures analogous to those known in the art. The amines of structure  $R^5R^6NH$  and  $R^7R^8NH$  are available commercially or can be prepared by standard techniques well known to those skilled in the art of organic chemistry.



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For example compounds of structure (II) in which  $R^1$  is  $OCH_3$ ,  $R^2$  to  $R^4$  are all hydrogen and X is chlorine can be prepared by the route outlined in Scheme I. It will be apparent to those skilled in the art that the reactions of Scheme I can also be carried out on compounds (A) in which  $R^1$  to  $R^4$  have different values to those indicated to produce further compounds of structure (II).

## Scheme I

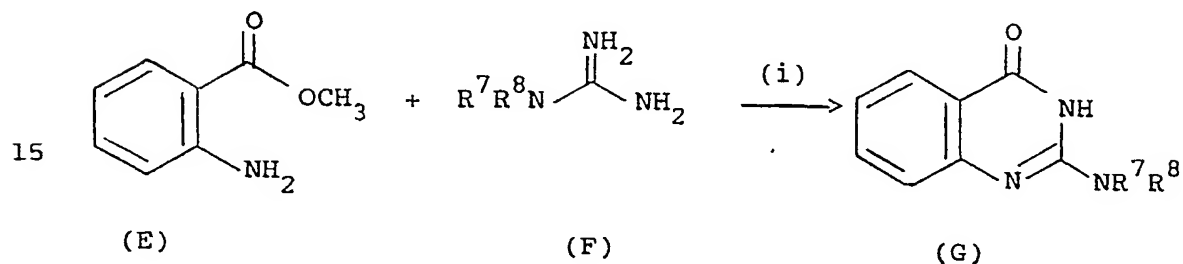


- (i)  $H_2$ , Pd/C 10%, EtOH
- (ii)  $KNCO$ , AcOH, NaOH
- (iii)  $POCl_3$ ,  $PhNMe_2$ ,  $\Delta$
- (iv)  $R^5R^6NH$ , NaOAc, THF/ $H_2O$ ,  $\Delta$ .

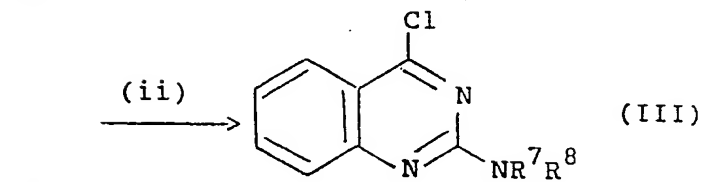
- 8 -

Compounds of structure (III) in which  $R^1$  to  $R^4$  are all hydrogen and  $R^7$  and  $R^8$  are both hydrogen,  $C_{1-4}$  alkyl or  $(CH_2)_n Ar^1$  or one is  $C_{1-4}$  alkyl and the other is  $(CH_2)_n Ar^1$  and X is chlorine can be prepared by the  
 5 procedures outlined in Scheme II. Again, it will be apparent to those skilled in the art that the reactions of Scheme (II) can be carried out on compounds (E) in which  $R^1$  to  $R^4$  are other than all hydrogen to product further compounds of structure (III).

10

Scheme II

20



30 (i)  $NaOCH_3$ ,  $nBuOH$

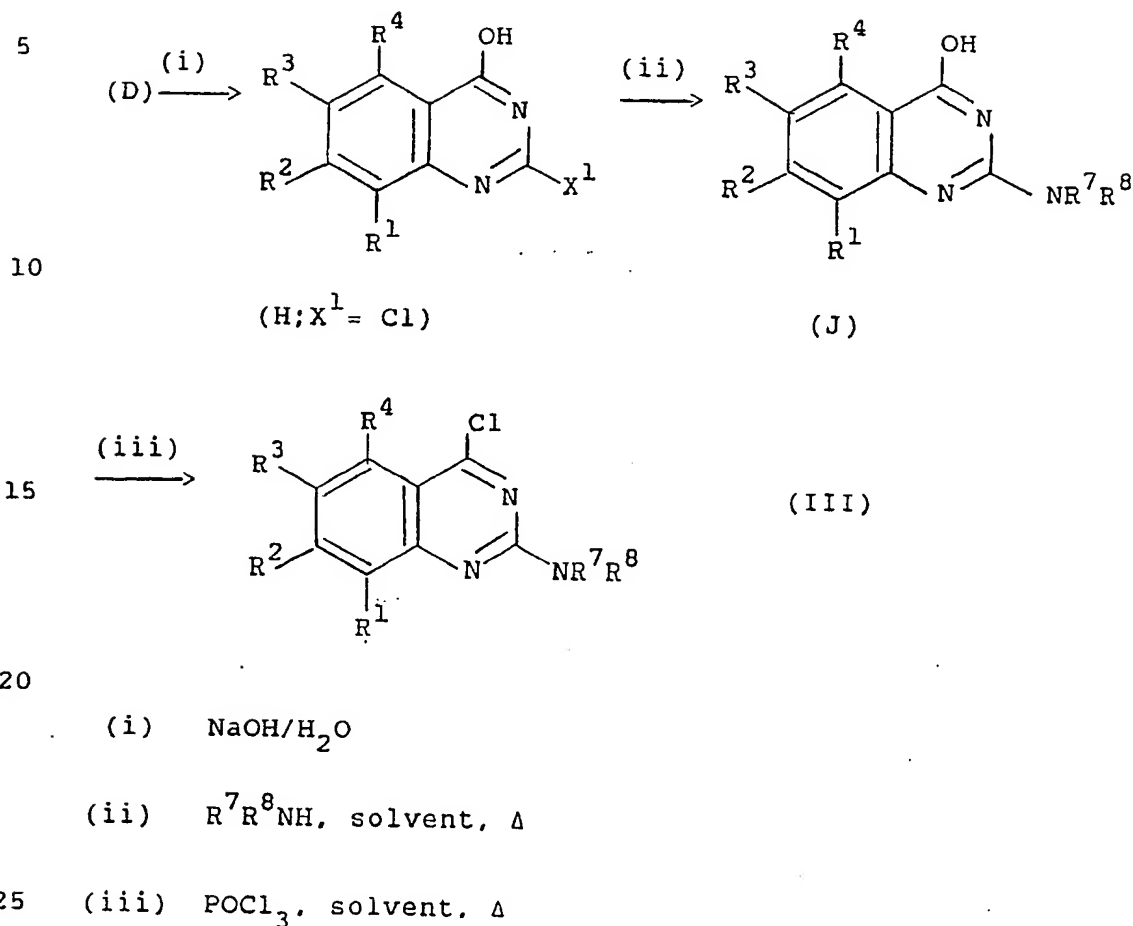
(ii)  $POCl_3$

35 Alternatively, compounds of structure (III) can be prepared from compounds of structure (D) - see Scheme I - by the method used in J. Med. Chem., 1981, 24, 127-140.

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This alternative method is outlined in Scheme III.

Scheme III



The starting materials used to prepare compounds of structures (II) and (III) are available commercially or can be prepared by standard techniques. In addition it will be appreciated that further variations of the above-noted schemes can be utilized, for example, in Scheme III, compounds of structure (H) in which X<sup>1</sup> is Cl can be replaced by compounds of structure (H) in which X<sup>1</sup> is, for example methylthio and then converted to compounds of structure (III) as shown. Such compounds in which X<sup>1</sup>

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is methylthio are prepared by standard techniques for example by treatment of the analogous thione precursor with methyl iodide in ethanol in the presence of sodium hydroxide; or, for example, when  $R^1$  to  $R^4$  are all H, are commercially available.

It is to be noted, and apparent to those skilled in the art that in the foregoing reactions, where necessary groups  $R^1$  to  $R^4$  and groups on aromatic rings Ar and  $Ar^1$  (e.g. hydroxy or amino groups) will be in "protected" form. For example, amino groups can be "protected" in the form of nitro groups and converted into amino groups as appropriate, and hydroxy groups can be protected using standard groups for example as described in "Greene, T.W., Protective Groups in Organic Chemistry" which also provides examples of further appropriate protective groups for other moities.

The compounds of structure (I) and their pharmaceutically acceptable salts exert an anti-secretory effect by inhibition of the gastrointestinal  $H^+K^+ATPase$  enzyme (Fellenius E., Berglindh T., Sachs G., Olke L., Elander B., Sjostrand S.E., and Wallmark B., 1981, Nature, 290, 159-61).

In a further aspect therefore the present invention provides compounds of structure (I) and pharmaceutically acceptable salts thereof for use in therapy.

The compounds of structure (I) and their pharmaceutically acceptable salts inhibit exogenously and endogenously stimulated gastric acid secretion and are useful in the treatment of gastrointestinal diseases in mammals, in particular humans. Such diseases include, for example, gastric and duodenal ulcers, and Zollinger-Ellison Syndrome. Further, the compounds of structure (I) can be

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used in the treatment of other disorders where an anti-secretory effect is desirable for example in patients with gastritis, NSAID induced gastritis, gastric ulcers, acute upper intestinal bleeding, in patients with a  
5 history of chronic and excessive alcohol consumption, and in patients with gastro oesophageal reflux disease (GERD).

In therapeutic use, the compounds of the present invention are usually administered in a standard  
10 pharmaceutical composition. The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

15 The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and  
20 lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for  
25 example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

30 A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

35

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A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The present invention also provides a method of inhibiting gastric acid secretion which comprises

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administering to a mammal in need thereof an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt thereof; and a method of treatment of diseases of the stomach or intestine based on increased acid secretion which comprises administering to a mammal in need thereof an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt thereof.

10       The pharmaceutically acceptable compounds of the invention will normally be administered to a subject for the treatment of gastrointestinal diseases and other conditions caused or exacerbated by gastric acidity. The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

25       In addition, the compounds of the present invention can be co-administered with further active ingredients, such as antacids (for example magnesium carbonate or hydroxide and aluminium hydroxide), non-steroidal anti-inflammatory drugs (for example indomethacin, aspirin or naproxen), steroids, or nitrite scavengers (for example ascorbic acid or aminosulphonic acid), or other drugs used for treating gastric ulcers (for example pirenzepine, prostanoids for example 16,16 dimethyl PGE<sub>2</sub>, or histamine H<sub>2</sub>-antagonists (for example, cimetidine).

35       The following examples illustrate the invention. Temperatures are recorded in degrees centigrade.

- 14 -

Example 1Preparation of 2-amino-8-methoxy-4-(2-methylphenylamino)-quinazoline

5

## A. Preparation of 3-methoxyanthranilic acid

2-Nitro-3-methoxybenzoic acid (10 g, 0.051 mol) was suspended in ethanol with palladium/charcoal 10% (1 g).  
10 The mixture was placed under hydrogen (50 psi) and shaken on a Parr until theoretical uptake had been achieved. The suspension was then flushed with nitrogen, the charcoal filtered off, and the filtrate evaporated in vacuo to give  
15 3-methoxyanthranilic acid (7.76 g, 91%) m.p. 172-175°C.

## B. Preparation of 8-methoxy-2,4-quinazolinedione

3-Methoxyanthranilic acid (6 g, 0.036 mol) was suspended in water (200 ml, 35°C) and glacial acetic acid  
20 (2.2 ml). A freshly prepared solution of potassium cyanate (3.7 g, 0.046 mol) in water (20 ml) was added dropwise to the stirred mixture. After 2 hours, sodium hydroxide (48.5 g 1.21 mol) was added in portions keeping the temperature below 40°C. A clear solution was obtained  
25 momentarily before precipitating the hydrated sodium salt. After cooling, the precipitate was filtered off, dissolved in hot water which was acidified to pH 5, causing precipitation of 8-methoxy-2,4-quinazolinedione (4.6 g, 58%) m.p. 255-257°C.

30

## C. Preparation of 8-methoxy-2,4-dichloroquinazoline

A suspension of 8-methoxy-2,4-quinazolinedione (4 g, 0.019 mol) suspended in phosphoryl chloride (10 ml  
35 0.108 mol) and N,N-dimethylaniline (1.6 ml, 0.0125 mol) was heated under reflux for 5 hours. The reaction



- 15 -

mixture was poured onto ice and the precipitate washed and dried to give 8-methoxy-2,4-dichloroquinazoline (3.79 g, 87%) m.p. 155-157°C.

5           D. Preparation of 8-methoxy-4-(2-methylphenyl-amino)-2-chloroquinazoline

8-Methoxy-2,4-dichloroquinazoline (3.7 g, 0.016 mol) was stirred in a mixture of water (85 ml), tetrahydrofuran  
10 (125 ml), o-toluidine (1.7 g, 0.016 mol) and sodium acetate (2.2 g, 0.027 mol) for a total of 4 days with heating to 50°C for a total of 32 hours and the addition of a total of 20 ml 0.01 mol NaOH dropwise over this period maintaining the pH at 7. The reaction mixture was evaporated in vacuo  
15 and crystallized from ethanol/water to give 8-methoxy-4-(2-methylphenylamino)-2-chloroquinazoline (2.89 g, 60%) m.p. 218-220°C.

20           E. Preparation of 2-amino-4-(2-methylphenylamino)-8-methoxyquinazoline

8-Methoxy-4-(2-methylphenylamino)-2-chloroquinazoline (1.8 g, 0.006 mol) was dissolved in ethanolic ammonia and heated in a sealed vessel at 120°C for 3 hours. After  
25 cooling, removal of excess solvent and chromatography (silica gel, 2% methanolic ammonia in chloroform) the 2-amino-4-(2-methylphenylamino)-8-methoxyquinazoline was isolated as crystals (0.52 g, 31%) from ethanol, m.p. 218-220°C.

30

$C_{16}H_{16}N_4O \cdot 0.37EtOH$

Found	C 67.61, H 6.26, N 18.81
Requires	C 67.61, H 6.17, N 18.84

35

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Example 2Preparation of 2-amino-8-methoxy-4-benzylaminoquinazoline

5

A. Preparation of 2-chloro-8-methoxy-4-benzylamino-quinazoline

Substituting benzylamine (1.4 g) for o-toluidine and  
10 using corresponding molar proportions in Example 1D gave,  
2-chloro-8-methoxy-4-benzylaminoquinazoline (3.2 g, 82%)  
m.p. 253-254°C.

B. Preparation of 2-amino-8-methoxy-4-benzylamino-  
15 quinazoline

Substituting 2-chloro-8-methoxy-4-benzylamino-  
quinazoline (2 g, 0.0067 mol) for 2-chloro-8-methoxy-4-  
(2-methylphenylamino)quinazoline and using corresponding  
20 molar proportions of the other reagents in Example 1E,  
gave 2-amino-8-methoxy-4-benzylaminoquinazoline (0.29 g,  
15%) from ethanol, m.p. 243-245°C.

$C_{16}H_{16}N_4O$

Found	C 68.77, H 5.52, N 20.16
25 Requires	C 68.55, H 5.75, N 19.99

Example 3

30 Preparation of 2-amino-8-methoxy-4-(2-methyl-4-  
methoxyphenylamino)quinazoline

A. Preparation of 2-chloro-8-methoxy-4-(2-methyl-4-  
methoxyphenylamino)quinazoline

35 Substituting 4-methoxy-o-toluidine (1.6 g, 0.0122 mol)  
for o-toluidine and using corresponding molar proportions

- 17 -

of the other reagents in Example 1D, gave 2-chloro-8-methoxy-4-(4-methoxy-2-methylphenylamino)quinazoline (2.02 g, 51%) m.p. 230-232°C.

- 5           B. Preparation of 2-amino-8-methoxy-4-(2-methyl-4-methoxyphenylamino)quinazoline

          Substituting 2-chloro-8-methoxy-4-(2-methyl-4-methoxyphenylamino)quinazoline (2.0 g, 0.006 mol) for  
10 2-chloro-8-methoxy-4-(2-methylphenylamino)quinazoline and using corresponding molar proportions of the other reagents in the Example 1E, gave 2-amino-8-methoxy-4-(2-methyl-4-methoxyphenylamino)quinazoline (0.25 g, 13%) from ethanol/water, m.p. 185-187°C.

15

		$C_{17}H_{18}N_4O_2 \cdot 0.5 H_2O$
Found	C 63.95, H 5.77, N 17.52	
Requires	C 63.93, H 5.99, N 17.54	

20

Example 4

Preparation of 2-amino-8-methoxy-4-(2-methylbenzylamino)-quinazoline

- 25           A. Preparation of 2-chloro-8-methoxy-4-(2-methylbenzylamino)quinazoline.

          Substituting 2-methylbenzylamine for o-toluidine (1.41 g, 0.0117 mol) and using corresponding molar  
30 proportions of the other reagents in the Example 1D, gave 2-chloro-8-methoxy-4-(2-methylbenzylamino)quinazoline (3.36 g, 89%) m.p. 279-281 °C.

- B. Preparation of 2-amino-8-methoxy-4-(2-methylbenzylamino)quinazoline  
35

- 18 -

Substituting 2-chloro-8-methoxy-4-(2-methylbenzyl-amino)quinazoline (2.3 g, 0.0073 mol) for 2-chloro-8-methoxy-4-(2-methylphenylamino)quinazoline in Example 1E, gave 2-amino-8-methoxy-4-(2-methylbenzylamino)quinazoline (0.4 g, 18.5%) from acetonitrile, m.p. 274-275°C.

Found  $C_{17}H_{18}N_4O \cdot 0.67H_2O \cdot 0.36CH_3CN$   
C 68.78, H 6.20, N, 19.07  
Requires C 69.03, N 6.19, N, 19.03

#### Example 5

##### Preparation of 2-dimethylamino-8-methoxy-4-(2-methylphenyl-amino)quinazoline

A. Preparation of 2-dimethylamino-8-methoxy-4-(2-methylphenylamino)quinazoline

Substituting ethanolic dimethylamine for ethanolic ammonia and using corresponding molar proportions of the other reagents in the Example 1E, gave 2-dimethylamino-8-methoxy-4-(2-methylphenylamino)quinazoline (0.73 g, 59%) from acetonitrile, m.p. 141-143°C.

Found  $C_{18}H_{20}N_4O \cdot 0.2H_2O$   
C 69.37, H 6.34, N 18.01  
Requires C 69.30, H 6.59, N 17.96

#### Example 6

##### Preparation of 2-amino-8-methyl-4-(2-methylphenylamino)-quinazoline

A. Preparation of 8-methyl-2,4-quinazolone

- 19 -

Substituting 3-methylantranilic acid (5 g, 0.033 mol) for 3-methoxyantranilic acid and using corresponding molar proportions of the other reagents in Example 1B gave 8-methyl-2,4-quinazolinedione (4.18 g, 72%), m.p. 285-287°C.

5

B. Preparation of 2,4-dichloro-8-methylquinazoline

Substituting 8-methyl-2,4-quinazolinedione (4.0 g, 0.023 mol) for 8-methoxy-2,4-quinazolinedione and using corresponding molar proportions of the other reagents in Example 1C, gave 2,4-dichloro-8-methylquinazoline (4.12 g, 84%), m.p. 180-230°C which was used without further purification.

10

15 C. Preparation of 2-chloro-8-methyl-4-(2-methylphenyl-amino)quinazoline

Substituting 2,4-dichloro-8-methyl-4-(2-methylphenyl-amino)quinazoline (3.7 g, 0.018 mol) for 2,4-dichloro-8-methoxyquinazoline and using corresponding molar proportions of the other reagents in Example 1D, gave 2-chloro-8-methyl-4-(2-methylphenylamino)quinazoline (3.96 g, 77%), m.p. 125-126°C.

20

25 D. Preparation of 2-amino-8-methyl-4-(2-methylphenyl-amino)quinazoline

Substituting 2-chloro-8-methyl-4-(2-methylphenyl-amino)quinazoline (2.0 g, 0.007 mol) for 2-chloro-8-methoxy-4-(2-methylphenylamino)quinazoline and using corresponding molar proportions of the other reagents in Example 1E, gave 2-amino-8-methyl-4-(2-methylphenyl-amino)quinazoline (0.27 g, 15.3%) from acetonitrile/water, m.p. 118-120°C.

30

35

- 20 -

$C_{16}H_{16}N_4$

Found	C 72.59, H 6.21, N 21.17
Requires	C 72.70, H 6.10, N 21.20

5

Example 7Preparation of 2-amino-4-(2-methylphenylamino)quinazoline

10

## A. Preparation of 2-amino-4-(3H)-quinazolone

Guanidine hydrochloride (47.77 g, 0.5 mol) was added portionwise to a stirred suspension of sodium methoxide (32.42 g, 0.60 mol) in n-butanol (450 ml) at ambient temperature over 0.5 hour. After a further 0.5 hour a solution of methyl anthranilate (15 g, 0.10 mol) in n-butanol (150 ml) was added dropwise and then slowly brought to reflux. After distilling off ca. 100 ml of solvent the reaction mixture was heated under reflux at 116°C for 117 hours. The cooled suspension was filtered, excess solvent removed and the residue dissolved in water, acidified to pH 5 and extracted with diethyl ether. The aqueous suspension was reacidified to pH 5, filtered off, washed with water and dried. The solid was then triturated in methanol, filtered, washed with ether and dried to give 2-amino-4-(3H)-quinazolone (3.0 g, 19%) m.p. >300°C.

20

25

## B. Preparation of 2-amino-4-chloroquinazoline

30

2-Amino-4-(3H)-quinazolone (2.0 g, 0.0124 mol) was heated under reflux in phosphoryl chloride (19.02 g, 0.0124 mol) for 2.5 hours. The reaction mixture was partitioned between chloroform, ice and NaOH solution (pH 9) and the organic phase dried, filtered, excess solvent removed and the residue triturated with chloroform to give 2-amino-4-chloroquinazoline (0.42 g, 19%) m.p. 275-278°C.

35

- 21 -

C. Preparation of 2-amino-4-(2-methylphenylamino)-quinazoline

2-Amino-4-chloroquinazoline (0.64 g, 0.0036 mol) was heated to 170°C in o-toluidine (1 ml, 0.008 mol) for 1 hour. The reaction mixture was dissolved in ethanol, stripped and partitioned between chloroform and NaOH solution (pH 9). The organic solution was dried, filtered and excess solvent removed to give an oil which afforded crystals of 2-amino-4-(2-methylphenylamino)quinazoline (0.55 g, 62%) m.p. 273-275°C (from ethanol).

		$C_{15}H_{14}N_4$	0.02CHCl <sub>3</sub>
Found	C	71.08	H 5.42, N 22.04
15 Requires	C	71.36	H 5.59, N 22.16

Example 8

Preparation of 2-pyrrolidino-4-(2-methylphenylamino)-quinazoline

A. Preparation of 2-chloro-4-(2-methylphenylamino)-quinazoline

Substituting 2,4-dichloroquinazoline (9.95 g, 0.05 mol) for 8-methoxy-2,4-dichloroquinazoline and using corresponding molar proportions of the other reagents in Example 1D, gave 2-chloro-4-(2-methylphenylamino)-quinazoline (10.19 g, 76%) m.p. 192-194°C.

B. Preparation of 2-pyrrolidino-4-(2-methylphenylamino)quinazoline

2-chloro-4-(2-methylphenylamino)quinazoline (5 g, 0.0185 mol) and pyrrolidine (6.59 g, 0.093 mol) were dissolved in ethanol (65 ml) placed in a sealed vessel

- 22 -

and heated to 135°C for 5 hours. After cooling, the reaction mixture was dissolved in ethanol and then evaporated in vacuo. The oily residue afforded crystals of 2-pyrrolidino-4-(2-methylphenylamino)quinazoline (3.67 g, 65%) from ethanol/water, m.p. 152-154°C.

$C_{19}H_{20}N_4$

Found        C 74.58, H 6.60, N 18.49  
Requires    C 74.97, H 6.62, N 18.41

10

#### Example 9

##### Preparation of 2-ethylamino-4-(2-methylphenylamino)-quinazoline

15

2-Chloro-4-(2-methylphenylaminomethyl)quinazoline (5.00 g, 0.0185 mol) and ethylamine in ethanol (33%, 30 ml) were dissolved in ethanol (35 ml) placed in a sealed vessel and heated for 5 hours at 130°C. After cooling and removal of excess solvent in vacuo the residue afforded crystals of 2-ethylamino-4-(2-methylphenylamino)-quinazoline (1.7 g, 33%) from ethanol/water, m.p. 127-129°C.

25

$C_{17}H_{18}N_4$

Found        C 73.09, H 6.43, N 20.06  
Requires    C 73.35, H 6.52, N 20.13

#### Example 10

30

##### Preparation of 2-benzylamino-4-(2-methylphenylamino)-quinazoline

2-Chloro-4-(2-methylphenylamino)quinazoline (2.7 g, 0.01 mol) and benzylamine (2.4 g, 0.022 mol) were dissolved in n-butanol (20 ml) and heated under reflux for 5 hours.



- 23 -

The solution was cooled, excess solvent removed in vacuo and the residue treated with water, filtered and crystallised from ethanol/water. The compound was then chromatographed (silica gel; 0.5% methanolic ammonia/  
5 chloroform) to afford an oil, which on trituration with ether gave crystals of 2-benzylamino-4-(2-methylphenyl-amino)quinazoline (1.88 g, 55%), m.p. 127-130°C.

10 Found  $C_{22}H_{20}N_4$  C 77.50, H 6.00, N 16.45  
Requires C 77.62, H 5.92, N 16.46

#### Example 11

15 Preparation of 2-amino-4-(2-methylphenylamino)-6-ethyl-quinazoline

A. Preparation of 6-ethyl-2,4-quinazoline dione

20 Substituting 6-ethylanthranilic acid for 3-methoxyanthranilic acid and using corresponding molar proportions of the other reagents in Example 1B, gave 6-ethyl-2,4-quinazoline dione (20.15 g, 90%) m.p. 325°C.

25 B. Preparation of 6-ethyl-2,4-dichloroquinazoline

Substituting 6-ethyl-2,4-quinazolinedione (20 g, 0.105 mol) for 8-methoxy-2,4-quinazolinedione and using corresponding molar proportions of the other reagents in  
30 Example 1C, gave 6-ethyl-2,4-dichloroquinazoline (19.57 g, 82%) m.p. 90-92°C.

C. Preparation of 2-chloro-4-(2-methylphenylamino)-6-ethylquinazoline

35

- 24 -

Substituting 6-ethyl-2,4-dichloroquinazoline (10.0 g, 0.044 mol) for 8-methoxy-2,4-dichloroquinazoline and using corresponding molar proportions of the other reagents in Example 1D, gave 2-chloro-4-(2-methylphenylamino)-6-ethylquinazoline (7.23 g, 56%) m.p. 177-179°C.

D. Preparation of 2-amino-4-(2-methylphenylamino)-6-ethylquinazoline

Substituting 2-chloro-4-(2-methylphenylamino)-6-ethylquinazoline (2.98 g, 0.01 mol) for 8-methoxy-2-chloro-4-(2-methylphenylamino)quinazoline and using corresponding molar proportions of the other reagents in Example 1E, gave 2-amino-4-(2-methylphenylamino)-6-ethylquinazoline (0.76 g, 27%) from ether, m.p. 263-265°C.

$C_{17}H_{18}N_4$  1.5% w/w  $CHCl_3$   
Found C 72.18, H 6.49, N 19.76  
Requires C 72.40, H 6.43, N 19.83

Example 12

Preparation of 8-methoxy-2,4-bis(2-methylphenylamino)-quinazoline

8-methoxy-4-(2-methylphenylamino)-2-chloroquinazoline (1.00 g, 0.0033 mol) was dissolved in ethanol (15 ml) with o-toluidine (1.06 g, 0.0099 mol) and heated in a sealed vessel at 150°C for 5 hours. After cooling and removal of excess solvent in vacuo the solid was chromatographed (silica gel, chloroform). 8-Methoxy-2,4-bis(2-methylphenylamino)quinazoline was isolated as crystals (0.93 g, 76%) from ethanol/water, m.p. 185-187°C.

$C_{23}H_{22}N_4O$   
Found C 74.48, H 6.00, N 14.92  
Requires C 74.57, H 5.99, N 15.12

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Example 13Preparation of 2-methylamino-8-methoxy-4-(2-methylphenyl-amino)quinazoline

5

Substituting ethanolic methylamine for ethanolic ammonia and using corresponding molar proportions of the other reagents in the Example 1E, gave 2-methylamino-8-methoxy-4-(2-methylphenylamino)quinazoline (0.3 g, 35%) from ethanol/water, m.p. 190-192°C.

10

$C_{17}H_{18}N_4O$

Found	C 69.24, H 6.07, N 18.81
Requires	C 69.37, H 6.16, N 19.04

15

Example 14Preparation of 2-benzylamino-8-methoxy-4-(2-methylphenyl-amino)quinazoline

20

Substituting benzylamine (0.53 g 0.00495 mol) for o-toluidine and using corresponding molar proportions of the other reagents in Example 12 gave 2-benzylamino-8-methoxy-4-(2-methylphenylamino)quinazoline hydrochloride (0.62 g, 46%) from ethanolic HCl, m.p. 237-238°C.

25

$C_{23}H_{22}N_4O \cdot HCl \cdot 0.5H_2O$

Found	C 65.65, H 5.69, N 13.41, Cl 8.3
Requires	C 67.42, H 5.81, N 13.47, Cl 8.52

30

Example 15Preparation of 2-pyrrolidino-8-methoxy-4-(2-methylphenyl-amino)quinazoline

35

Substituting pyrrolidine (2.1 g, 0.03 mol) for o-toluidine and using corresponding molar proportions of

- 26 -

the other reagents in Example 12 gave 2-pyrrolidino-8-methoxy-4-(2-methylphenylamino)quinazoline (1.71 g, 77%) from ethanol, m.p. 181-183°C.

5

$C_{20}H_{22}N_4O$

Found	C 71.55, H 6.75, N 16.60
Requires	C 71.83, H 6.63, N 16.75

#### Example 16

10

#### Preparation of 2-phenylethylamino-4-(2-methylphenylamino)-quinazoline

Substituting phenylethylamine (3.64 g, 0.03 mol) for benzylamine and using corresponding molar proportions of the other reagents in Example 10 and using ethanol as the solvent gave 2-phenylethylamino-4-(2-methylphenylamino)-quinazoline (1.45 g, 58%) from ether, m.p. 95-96°C.

20

$C_{23}H_{22}N_4 \cdot 0.15H_2O$

Found	C 77.39, H 6.24, N 15.71
Requires	C 77.34, H 6.29, N 15.68

#### Example 17

25

#### Preparation of 8-methyl-4-(2-methylphenylamino)-2-(2-phenylethylamino)quinazoline hydrochloride

8-Methyl-4-(2-methylphenylamino)-2-chloroquinazoline (0.71 g, 0.0025 mol) was dissolved in ethanol (20 ml) with 2-phenylethylamine (0.61 g, 0.005 mol) and heated in a sealed vessel at 140°C for 4 hours. After cooling and removal of excess solvent in vacuo the glass was dissolved in a small amount of methanol and 2N HCl added to form the hydrochloride salt which was recrystallized from ethanol/ether to give 8-methyl-4-(2-methylphenylamino)-

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2-(2-phenylethylamino)quinazoline hydrochloride (0.5 g, 50%), m.p.  $>250^{\circ}\text{C}$ .

$C_{24}H_{24}N_4 \cdot 1.0HCl$

5	Found	C 71.28, H 6.35, N 13.82, Cl 8.77
	Requires	C 71.18, H 6.22, N 13.84, Cl 8.76

### Example 18

10 Preparation of 2-amino-8-methoxy-4-(2-methoxyphenylamino)-  
quinazoline

A. Preparation of 2-chloro-8-methoxy-4-(2-methoxyphenylamino)quinazoline

Substituting o-anisidine (2.94 g) for o-toluidine and using corresponding molar proportions of the other reagents in Example 1D gave, 2-chloro-8-methoxy-4-(2-methoxyphenyl-amino)quinazoline (6.74 g, 98%) m.p. 194-196°C.

B. Preparation of 2-amino-8-methoxy-4-(2-methoxyphenylamino)quinazoline

Substituting 2-chloro-8-methoxy-4-(2-methoxyphenyl-  
25 amino)quinazoline (4.0 g) for 2-chloro-8-methoxy-4-(2-  
methylphenylamino)quinazoline and using corresponding  
molar proportions of the other reagents in Example 1E  
gave, after recrystallisation from ethanol/water  
2-amino-8-methoxy-4-(2-methoxyphenylamino)quinazoline  
30 (0.16 g, 4.2%), m.p. 243-244°C.

$C_{16}H_{16}N_4O_2 \cdot 0.18 H_2O$

Found	C 63.88, H 5.38, N 18.87
Requires	C 64.14, H 5.50, N 18.70.

35

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Example 19Preparation of 2,4-Bis-(N-methylphenylamino)-8-methoxy-quinazoline

5

8-Methoxy-2,4-dichloroquinazoline (1.5 g, 0.007 mol) was heated under reflux in a solution of N-methyl aniline (1.43 ml, 0.014 mol) in tetrahydrofuran (50 ml) for 16 hours precipitating a solid, which was collected and  
10 crystallised from ethanol/water to give 2,4-bis-(N-methylphenylamino)-8-methoxyquinazoline (0.37 g, 15%), m.p. 169-170°C.

$C_{23}H_{22}N_4O$   
15 Found C 74.32, H 5.85, N 15.04.  
Requires C 74.57, H 5.99, N 15.12.

Example 20

20 Preparation of 2,4-Bis-(N-methylphenylamino)quinazoline hydrochloride

Substituting 2,4-dichloroquinazoline (4.5 g, 0.0226 mol) for 8-methoxy-2,4-dichloroquinazoline and using  
25 corresponding molar proportions of the other reagents in Example 20, gave after crystallisation from ethanolic hydrogen chloride 2,4-bis-(N-methylphenylamino)-quinazoline hydrochloride (2.2 g, 30%), m.p. 243-244°C.

30  $C_{22}H_{20}N_4 \cdot 1.OHCl$   
Found C 69.79, H 5.56, N 14.72, Cl 9.02  
Requires C 69.89, H 5.70, N 14.68, Cl 9.29

35

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Example 21Preparation of 2-(N-methylphenylamino)-4-(2-methyl-phenylamino)-8-methoxyquinazoline

5

Substituting N-methylaniline (1.4 g, 0.013 mol) for o-toluidine and using the corresponding molar proportions of the other reagents in Example 12 gave after crystallisation from ethanol 2-(N-methylphenylamino)-4-(2-methylphenylamino)quinazoline (0.45 g, 45%), m.p. 145-147°C.

$C_{23}H_{22}N_4O$

Found            C 74.89, H 6.10, N 15.34.

15 Requires       C 74.57, H 5.99, N 15.12.

Example 22

20 Preparation of 2-(N-methylphenylamino)-4-(2-methyl-phenylamino)quinazoline hydrochloride

Substituting N-methylaniline (2.39 g, 0.022 mol) for benzylamine and using corresponding molar proportions of the other reagents in Example 10 and using ethanol as the solvent gave after crystallisation from ethanolic hydrogen chloride 2-(N-methylphenylamino)-4-(2-methylphenylamino)-quinazoline hydrochloride (1.64 g, 39%), m.p. 284-286°C.

$C_{22}H_{20}N_4 \cdot 1.OHCl$

30 Found            C 70.06, H 5.73, N 14.83, Cl 9.17

Requires       C 70.11, H 5.62, N 14.87, Cl 9.41

35

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Example 23Preparation of 2-phenethylamino-4-(2-methylphenylamino)-8-methoxyquinazoline hydrochloride

5

Substituting phenylethylamine (1.2 ml, 0.009 mol) for o-toluidine and using corresponding molar proportions of the other reagents in Example 12, gave after crystallisation from ethanolic hydrogen chloride/ether

10 2-phenethylamino-4-(2-methylphenylamino)-8-methoxyquinazoline hydrochloride (0.38 g, 42%), m.p. 263-265°C.

$C_{24}H_{24}N_4O \cdot 1.0HCl$

Found            C 68.62, H 6.06, N 13.64, Cl 8.22

15 Requires       C 68.48, H 5.99, N 13.31, Cl 8.42

Example 24

20 Preparation of 4-(N-methylphenylamino)-2-(2-methylphenylamino)-8-methoxyquinazoline

A. Preparation of 8-methoxy-4-(N-methylphenylamino)-2-chloroquinazoline

25 Substituting N-methylaniline (3.85 g, 0.036 mol) for o-toluidine and using corresponding molar proportions of the other reagents in Example 1D, gave after crystallisation from ethanol/water 8-methoxy-4-(N-methylphenylamino)-2-chloroquinazoline (6.19 g, 63%), m.p.

30 115-117°C.

B. Preparation of 8-methoxy-4-(N-methylphenylamino)-2-(2-methylphenylamino)quinazoline hydrochloride

35



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Substituting 8-methoxy-4-(N-methylphenylamino)-2-chloroquinazoline (1.5 g, 0.005 mol) for 8-methoxy-4-(2-methylphenylamino)-2-chloroquinazoline and using corresponding molar proportions of the other reagents in Example 12, gave after crystallisation from ethanolic hydrogen chloride/ether 4-(N-methylphenylamino)-2-(2-methylphenylamino)-8-methoxyquinazoline hydrochloride (0.99 g, 49%), m.p. 232-234°C.

10  $C_{23}H_{22}N_4O \cdot 1.0HCl$   
Found C 67.74, H 5.63, N 13.76, Cl 8.39  
Requires C 67.89, H 5.70, N 13.77, Cl 8.71

#### Example 25

15 Preparation of 2-amino-4-(2-methylbenzylamino)quinazoline

A. Preparation of 2-chloro-4-(2-methylbenzylamino)-  
20 quinazoline

2,4-Dichloroquinazoline (3.0g 0.015 mol) was stirred in a mixture of water (60 ml), tetrahydrofuran (100 ml), o-methylbenzylamine (1.83 g, 0.015 mol) and sodium acetate  
25 (1.38 g, 0.017 mol) for a total of 16 hours. The reaction mixture was evaporated under reduced pressure and crystallized from ethanol to give 2-chloro-4-(2-methylbenzylamino)quinazoline (1.44 g, 30%) m.p. 215-217°C.

30 B. Preparation of 2-amino-4-(2-methylbenzylamino)-quinazoline hydrochloride

Substituting 2-chloro-4-(2-methylbenzylamino)-quinazoline (1.3 g, 0.004 mol) for 2-chloro-4-(2-methylphenylamino)-8-methoxyquinazoline and using corresponding  
35 molar proportions of the other reagents in the Example 1E

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gave after crystallisation from ethanolic hydrogen chloride/ether 2-amino-4-(2-methylbenzylamino)quinazoline hydrochloride (0.5 g, 42%), m.p. 258-260°C.

5  $C_{16}H_{16}N_4 \cdot 1.0HCl \cdot 0.1H_2O$   
 Found C 63.41, H 5.69, N 18.54, Cl 11.90  
 Requires C 63.51, H 5.73, N 18.51, Cl 11.71

### Example 26

Preparation of 2-(2-methylphenylamino)-4-(N-methyl-phenylamino)quinazoline hydrochloride

A. Preparation of 2-chloro-4-(N-methylphenylamino)-  
15 quinazoline

Substituting N-methylphenylamine (9.9 g, 0.092 mol) for 2-methyl-benzylamine and using corresponding molar proportions of the other reagents in Example 25A, gave after crystallisation from ethanol/water 2-chloro-4-(N-methylphenylamino)quinazoline hydrochloride (24.47 g, 75%), m.p. >300°C.

B. Preparation of 2-(2-methylphenylamino)-4-(N-methylphenylamino)quinazoline hydrochloride

30 Substituting 2-chloro-4-(N-methylphenylamino)-quinazoline (2.0 g. 0.007 mol) for 2-chloro-8-methoxy-4-(2-methylphenylamino)quinazoline and using corresponding molar proportions of the other reagents in Example 12, gave after crystallisation from ethanolic hydrogen chloride 2-(2-methylphenylamino)-4-(N-methylphenylamino)-quinazoline hydrochloride (1.36 g, 48%), m.p. 255-257°C.

			$C_{22}H_{20}N_4 \cdot 1.0HCl$
35	Found	C 69.95, H 5.58, N 14.89, Cl 9.38	
	Requires	C 70.11, H 5.62, N 14.87, Cl 9.41	

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Example 27Preparation of 2-phenylamino-4-(N-methylphenylamino)-quinazoline hydrochloride

5

2-Chloro-4-(N-methylphenylamino)quinazoline (2.0 g, 0.007 mol) was dissolved in ethanol (20 ml) with aniline (1.37 g, 0.15 mol) and heated in a sealed vessel at 150°C for 5 hours. After cooling and removal of excess solvent  
10 in vacuo pressure the solid was treated with ethanolic hydrogen chloride to form the hydrochloride which was recrystallized from ethanol to give 2-phenylamino-4-(N-methylphenylamino)quinazoline hydrochloride (1.99 g, 74%), m.p. 265-267°C.

15

$C_{21}H_{18}N_4 \cdot 1.0HCl$

Found      C 69.28, H 5.17, N 15.35, Cl 9.78  
Requires   C 69.51, H 5.28, N 15.44, Cl 9.77

20

Example 28Preparation of 2-amino-4-(N-methylphenylamino)quinazoline hydrochloride

25

Substituting N-methylaniline (1.95 g, 0.0183 mol) for O-toluidine and using corresponding molar proportions of the other reagents in Example 7C, gave after crystallisation from ethanolic hydrogen chloride 2-amino-4-(N-methylphenylamino)quinazoline hydrochloride (0.27 g,  
30 13%), m.p. 190-192°C.

$C_{15}H_{14}N_4 \cdot 0.3H_2O \cdot 0.15HCl$

Found      C 68.43, H 5.48, N 21.59, Cl 2.17  
Requires   C 68.81, H 5.70, N 21.40, Cl 2.04

35

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Example 29Preparation of 2-amino-4-(N-methylphenylamino)-8-methoxy-quinazoline hydrochloride

5

Substituting 2-amino-4-chloro-8-methoxyquinazoline for 2-amino-4-chloroquinazoline and using corresponding molar proportions of the other reagents in Example 28, ... gave after crystallisation from ethanolic hydrogen chloride 2-amino-4-(N-methylphenylamino)-8-methoxy-quinazoline hydrochloride (0.27 g, 10%), m.p. 282-284°C.

10

$C_{16}H_{16}N_4O \cdot HCl$

Found	C 60.34, H 5.60, N 17.67, Cl 10.98
15 Requires	C 60.66, H 5.38, N 17.69, Cl 11.19

Example 30Preparation of 2-[(4-hydroxy-2-methylphenyl)amino]-4-(N-methylphenylamino) quinazoline hydrochloride

20

Substituting 4-hydroxy-2-methylaniline (1.8 g 0.0148 mol) for aniline and using corresponding molar proportions of the other reagents in Example 27, gave after crystallisation from ethanolic hydrogen chloride 2-[(4-hydroxy-2-methylphenyl)amino]quinazoline hydrochloride (0.72 g, 24%), m.p. 274-276°C.

25

$C_{22}H_{20}N_4O \cdot 1.0HCl$

30 Found	C 66.91, H 5.33, N 14.06, Cl 8.97
Requires	C 67.25, H 5.39, N 14.26, Cl 9.02

Example 31Preparation of 2-(2-methylbenzylamino)-4-(N-methylphenylamino)quinazoline hydrochloride

35

- 35 -

Substituting 2-methylbenzylamine (1.79 g, 0.0148 mol) for aniline and using corresponding molar proportions of the other reagents in Example 27, gave after crystallisation from ethanolic hydrogen chloride

5 2-(2-methylbenzylamino)-4-(N-methylphenylamino)quinazoline hydrochloride (0.61 g, 21%), m.p. 226-228°C.

$C_{23}H_{22}N_4 \cdot 1.0HCl$

Found C 70.44, H 5.90, N 14.36, Cl 9.08

10 Requires C 70.67, H 5.93, N 14.33, Cl 9.07

#### Example 32

Preparation of 2-[(2-methyl-4-fluorophenyl)amino]-

15 4-(N-methylphenylamino)quinazoline hydrochloride

Substituting 2-methyl-4-fluoroaniline (1.85 g, 0.0148 mol) for aniline and using corresponding molar proportions of the other reagents in Example 27, gave after

20 crystallisation from ethanolic hydrogen chloride 2-[(2-methyl-4-fluorophenyl)amino]-4-(N-methylphenylamino)-quinazoline hydrochloride (0.6 g, 15%), m.p. 243-245°C.

$C_{22}H_{19}N_4F \cdot 1.0HCl$

25 Found C 66.50, H 5.24, N 14.17, Cl 8.93

Requires C 66.92, H 5.11, N 14.19, Cl 8.98

#### Example 33

30 Preparation of 2-(2-methylphenylamino)-4-phenyl-  
aminoquinazoline hydrochloride

A. Preparation of 2-(2-methylphenylamino)-4-quinazolone

35

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2-Methylthio-4-quinazolone (10.0 g, 0.052 mol) was fused with o-toluidine (8.35 g, 0.078 mol) at 160°C. After 4 hours, the solid was treated with ethanol, and filtered to give 2-methylphenylamino)-4-quinazolone  
5 (10.7 g, 82%) m.p. 278-280°C.

B. Preparation of 4-chloro-2-(2-methylphenylamino)-quinazoline

10 2-(2-Methylphenylamino)-4-quinazolone (5.0 g, 0.0198 mol) was dissolved in phosphoryl chloride (20 ml, 0.216 mol) and N,N-dimethylaniline (3.5 ml, 0.025 mol) and refluxed for 3/4 hours. The reaction mixture was poured onto ice/N NaOH (100 ml) and the precipitate washed and  
15 dried to give 4-chloro-2-(2-methylphenylamino)quinazoline hydrochloride (5.79 g, 95%), used without purification.

C. Preparation of 2-(2-methylphenylamino)-4-phenylaminoquinazoline hydrochloride

20

4-Chloro-2-(2-methylphenylamino)quinazoline (1.5 g, 0.0048 mol) was dissolved in aniline (1.5 ml, 0.016 mol) and heated at 170°C for 1 hour. After cooling and evaporation of excess solvent the residue was crystallised  
25 from ethanolic hydrogen chloride to give 2-(2-methylphenylamino)-4-phenylaminoquinazoline hydrochloride. (0.30 g, 17%) m.p. 239-240°C.

30 Found  $C_{21}H_{18}N_4 \cdot 1.0HCl \cdot 0.19H_2O \cdot 0.02EtOH$   
C 68.96, H 5.31, N 15.42, Cl 9.59  
Requires C 68.71, H 5.37, N 15.22, Cl 9.63

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Example 34Preparation of 2-(2-methylphenylamino)-4-methylamino-quinazoline hydrochloride

5

2-(2-methylphenylamino)-4-chloroquinazoline (2 g, 0.0065 mol) and methylamine in ethanol (33%, 30 ml) were placed in a pressure vessel and heated for 4 hours at 140°C. After cooling, the reaction mixture was  
10 evaporated to dryness. The residue afforded crystals of 2-(2-methylphenylamino)-4-methylaminoquinazoline hydrochloride (0.29 g, 8.9%) from ethanolic hydrogen chloride, m.p. 275-279°C.

15

$C_{16}H_{16}N_4 \cdot HCl$

Found        C 63.70, H 5.56, N 18.58, Cl 11.76  
Requires    C 63.89, H 5.70, N 18.63, Cl 11.79

Example 35

20

Preparation of 2-(2-methylphenylamino)-4-propylamino-quinazoline hydrochloride

Substituting n-propylamine (1.77 g, 0.03 mol) for  
25 methylamine and using corresponding molar proportions of the other reagents in Example 34, gave after crystallisation 2-(2-methylphenylamino)-4-propylamino-quinazoline hydrochloride (0.67 g, 20.5%) from ethanolic hydrogen chloride, m.p. 215-217°C.

30

$C_{17}H_{18}N_4 \cdot HCl$

Found        C 65.12, H 6.20, N 17.83, Cl 11.20  
Requires    C 64.86, H 6.08, N 17.80, Cl 11.26

35

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Example 36Preparation of 2-(2-methylphenylamino)-4-(n-pentylamino)-quinazoline hydrochloride

5

Substituting amylamine (1.13 g, 0.013 mol) for methylamine and using corresponding molar proportions of the other reagents in Example 34, gave after crystallisation 2-(2-methylphenylamino)-4-(n-pentylamino)-quinazoline hydrochloride (0.24 g, 10.3%) from ethanolic hydrogen chloride/ether, m.p. 129-130°C.

$C_{20}H_{24}N_4 \cdot HCl$

Found	C 67.37, H 7.19, N 15.46, Cl 9.86
15 Requires	C 67.31, H 7.06, N 15.70, Cl 9.93

Example 37Preparation of 2-(2-methylphenylamino)-4-(2-methoxybenzylamino)quinazoline hydrochloride

20

Substituting 2-methoxybenzylamine (1.78 g, 0.0147 mol) for methylamine and using corresponding molar proportions of the other reagents in Example 34, gave after crystallisation 2-(2-methylphenylamino)-4-(2-methoxybenzylamino)quinazoline hydrochloride (1.52 g, 57.5%) from ethanolic hydrogen chloride, m.p. 218-220°C.

$C_{23}H_{22}N_4O \cdot HCl$

30

35



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Example 38Preparation of 2-(2-methylphenylamino)-4-N-piperidino-quinazoline hydrochloride

5

Substituting piperidine (1.25 g, 0.0147 mol) for methylamine and using corresponding molar proportions of the other reagents in Example 34, gave after crystallisation 2-(2-methylphenylamino)-4-N-piperidino-quinazoline hydrochloride (0.25 g, 10%) from ethanolic hydrogen chloride/ether, m.p. 218-220°C.

$C_{20}H_{22}N_4 \cdot HCl$

Found	C 67.48, H 6.51, N 15.63, Cl 9.94
15 Requires	C 67.69, H 6.53, N 15.79, Cl 9.99

Example 39Preparation of 2-(2-methylphenylamino)-4-N-morpholino-quinazoline hydrochloride

20

Substituting morpholine (1.28 g, 0.0147 mol) for methylamine and using corresponding molar proportions of the other reagents in Example 34, gave after crystallisation 2-(2-methylphenylamino)-4-N-morpholino-quinazoline hydrochloride (0.26 g, 11.2%), from ethanolic hydrogen chloride/ether, m.p. 244-246°C.

$C_{19}H_{20}N_4O \cdot HCl$

30 Found	C 64.04, H 6.03, N 15.80, Cl 10.04
Requires	C 63.95, H 5.93, N 15.70, Cl 9.94

35

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Example 40Preparation of 2-(2-methylphenylamino)-4-dimethylamino-quinazoline hydrochloride

5

Substituting dimethylamine (30 ml) for methylamine and using corresponding molar proportions of the other reagents in Example 34, gave after crystallisation 2-(2-methylphenylamino)-4-dimethylaminoquinazoline hydrochloride (0.29 g, 11.8%), m.p. 277-282°C decomp.

10

$C_{17}H_{18}N_4 \cdot HCl$

Found	C 65.10, H 6.20, N 17.83, Cl 11.20
Requires	C 64.86, H 6.08, N 17.80, Cl 11.26

15

Example 41Preparation of 2-(2-methyl-4-fluorophenylamino)-4-(N-methylphenylamino)-8-methoxyquinazoline hydrochloride

20

2-Chloro-4-N-methylphenylamino-8-methoxyquinazoline (0.8 g, 0.0026 mol) and 4-fluoro-2-methylaniline (0.66 g, 0.0053 mol) were dissolved in ethanol (20 ml) placed in a pressure vessel and heated for 4 hours at 150°C. After cooling the reaction mixture was evaporated to dryness. The residue afforded crystals of 2-(2-methyl-4-fluorophenylamino)-4-(N-methylphenylamino)-8-methoxyquinazoline hydrochloride (0.25 g, 22%) from ethanolic hydrogen chloride, m.p. 218-220°C.

25

30

$C_{23}H_{21}N_4FO \cdot HCl$

Found	C 64.87, H 5.19, N 13.05, Cl 8.16
Requires	C 65.01, H 5.22, N 13.19, Cl 8.34

35

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Example 42Preparation of 2-[(4-methoxy-2-methylphenyl)amino]-4-(N-methylphenylamino)quinazoline hydrochloride

5

A. Preparation of 2-[(4-methoxy-2-methylphenyl)-amino]quinazolin-4-one

10 Substituting 4-methoxy-2-methylaniline (5.48 g) for o-toluidine and using corresponding molar proportions of other reagents in Example 33A gave 2-[(4-methoxy-2-methylphenyl)amino]quinazolin-4-one (4.35 g, 77%) crystallised from methanol, m.p. 270-272°C.

15

B. Preparation of 4-chloro-2-[(4-methoxy-2-methylphenyl)amino]quinazoline

20 Substituting 2-[(4-methoxy-2-methylphenyl)amino]-quinazolin-4-one (3.6 g) for 2-(2-methylphenylamino)-quinazolin-4-one and using corresponding molar proportions of other reagents in Example 33B gave 4-chloro-2-[(4-methoxy-2-methylphenyl)amino]quinazoline (3.8 g) which was used without purification.

25

C. Preparation of 2-[(4-methoxy-2-methylphenyl)-amino]-4-(N-methylphenylamino)quinazoline hydrochloride

30 Substituting 4-chloro-2-[(4-methoxy-2-methylphenyl)-amino]quinazoline (3.8 g) for 4-chloro-2-[(2-methylphenyl)-amino]quinazoline and N-methylaniline for aniline in Example 33C gave the title compound (2.0 g, 38% - 2 steps) which was recrystallised from ethanol/diethyl ether as yellow needles, m.p. 248-250°C.

35 Found  $C_{23}H_{22}N_4O \cdot HCl \cdot 0.25 H_2O$   
C 67.01, H 5.72, N 13.52, Cl 8.33  
Requires C 67.14, H 5.76, N 13.62, Cl 8.62

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Example 43Preparation of 4-(N-methylphenylamino)-2-(2-methylphenylamino)-6-methoxyquinazoline hydrochloride

5

## A. 2,4-Dihydroxy-6-methoxyquinazoline

A mixture of 5-methoxy anthranilic acid (40 g, 0.24 M), acetic acid (18.0 g, 0.3 M) and 1 litre warm water (35°C) was stirred and allowed to cool. A solution of potassium cyanate (24.3 g, 0.3 M) in water (100 ml) was added over 15 minutes and then stirred for a further 30 minutes. Sodium hydroxide (320 g, 8.0 M) solid was added portionwise and the reaction was then heated at 90°C for 15 30 minutes and allowed to cool overnight. The solid was filtered off and dissolved in hot water (500 ml) and then acidified with dilute sulphuric acid to precipitate the product. The solid was filtered off and washed free of acid with water and then dried at 100°C/vacuum to yield 20 the title compound (37.7 g) m.p. >290°C.

## B. 2,4-Dichloro-6-methoxyquinazoline

2,4-Dihydroxy-6-methoxyquinazoline (37 g, 0.19 M), phosphoryl chloride (95 ml) and dimethylaniline (40 ml) were heated under reflux for 3 hours. After cooling the reaction mixture was poured onto ice and the precipitated solid was filtered off, washed with water and air dried. The product was used immediately in the next stage.

30

## C. 2-Chloro-4-(N-methylphenylamino)-6-methoxyquinazoline

A mixture of 2,4-dichloro-6-methoxyquinazoline, (38.3 g, 0.19 M assuming 100% yield from previous step), N-methylaniline (19.26 g, 0.18 M), sodium acetate (16.4 g,

35

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0.2 M) in tetrahydrofuran (2 litres) and water (1 litre) was stirred at room temperature for 8 days. Reaction was then concentrated to low volume (about 500 ml) and an oil separated out which solidified. The solid was filtered  
5 off and extracted with dichloromethane. Silica gel column chromatography followed by evaporation to dryness gave a residue which was washed with 40-60°C petroleum ether (to remove trace impurity) to yield title compound (31.25 g) m.p. 133-4°C.

10

D. Preparation of 4-(N-methylphenylamino)-2-(2-methylphenylamino)-6-methoxyquinazoline hydrochloride

A mixture of 2-chloro-4-(N-methylphenylamino)-6-methoxyquinazoline (5.4 g, 0.027 M), o-toluidine (4.28 g, 0.04 M) in ethanol (50 ml) was heated in a Berchhof  
15 pressure vessel at 140°C for 5 hours (maximum pressure 40 psi). After cooling, ethanol/HCl was added and the solid which crystallised out was filtered off and recrystallised  
20 from isopropanol/ether to yield the title compound (4.23 g, m.p. 258-260°C).

#### Example 44

25 4-(N-Methylphenylamino)-2-(2-methyl-4-fluorophenylamino)-6-methoxyquinazoline

2-Chloro-4-(N-methylphenylamino)-6-methoxyquinazoline (5.4 g, 0.02 M) and 4-fluoro-2-methylaniline (4.96 g, 0.04 M) were dissolved in ethanol (50 ml) and heated at  
30 140°C for 5 hours in a Berghof pressure reactor. The mixture was cooled and ethereal/HCl added. The precipitated solid was filtered off and recrystallised (isopropanol/ether followed by isopropanol) to yield the  
35 title compound (3.8 g) m.p. 248-250°C.

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Example 45Preparation of 2-(2-methylphenylamino)-4-(N-methyl-4-methoxyphenylamino)quinazoline hydrochloride

5

Substituting N-methyl-p-anisidine (3.18 g, 0.023 mol) for methylamine and using corresponding molar proportions of the other reagents in Example 34, gave after crystallisation 2-(2-methylphenylamino)-4-(N-methyl-4-methoxyphenylamino)quinazoline hydrochloride (2.45 g, 33%), from ethanolic hydrogen chloride, m.p. 224-226°C.

Example 46

15 Preparation of 2-(2-methylphenylamino)-4-(N-methyl-4-hydroxyphenylamino)quinazoline hydrochloride

2-(2-Methylphenylamino)-4-(N-methyl-4-methoxyphenylamino)quinazoline hydrochloride (1.6 g, 0.0043 mol) was stirred in dry dichloromethane (50 ml) at 0-5°C under nitrogen. To this solution was added boron tribromide (2.0 ml, 0.0216 mol) dropwise at 0-5°C over 10 minutes. The mixture was stirred for 3 hours at 0-5°C and then allowed to reach room temperature over 16 hours. After pouring onto ice, basifying and neutralising the aqueous phase was extracted with dichloromethane, the organic extracts which dried and evaporated to dryness. The residue afforded crystals of 2-(2-methylphenylamino)-4-(n-methyl-4-hydroxyphenylamino)quinazoline hydrochloride (0.4 g, 23.7%) from ethanolic hydrogen chloride m.p. 317-319°C.

35

- 45 -

Example 47Preparation of 2-[(4-chloro-2-methylphenyl)amino]-4-(N-methylphenylamino)quinazoline hydrochloride.

5

A. Preparation of 2-[(4-chloro-2-methylphenyl)-amino]-4-(N-methylphenylamino)quinazolone.

Substituting 2-methyl-4-chloroaniline (2.6 g) for  
10 o-toluidine and using corresponding molar proportions of the other reagents in Example 33A gave the title compound (2.73 g), m.p. >270°C (dec).

B. Preparation of 4-chloro-2-[(4-chloro-2-methyl-phenyl)amino]quinazoline.  
15

Substituting 2-[(4-chloro-2-methylphenyl)amino]-4-quinazolone (2.5 g) for 2-[(2-methylphenyl)amino]-4-quinazolone and using corresponding molar proportions of  
20 the other reagents in Example 33B gave the title compound (1.0 g) which was used without purification.

C. Preparation of 2-[(4-chloro-2-methylphenyl)-amino]-4-(N-methylphenylamino)quinazoline hydrochloride  
25

Substituting 4-chloro-2-[(4-chloro-2-methylphenyl)-amino]quinazoline (1.0 g) and N-methylaniline (1.0 g) for the reagents in Example 33C and using analogous conditions and work-up gave the title compound (0.17 g), m.p.  
30 263-265°C, after two recrystallisations from ethanol/diethyl ether.

35

- 46 -

Example 48Preparation of 2-(2-methylphenylamino)-4-(N-methylphenylamino)-8-fluoroquinazoline hydrochloride

5

In a procedure analogous to that of Example 41 2-chloro-4-(N-methylphenylamino)-8-fluoroquinazoline and o-toluidine are reacted together to give the title compound. The starting 2-chloro-4-(N-methylphenylamino)-  
10 8-fluoroquinazoline is prepared via procedures analogous to those of Example 1.

Example 49

15 Preparation of 2-(2-methyl-4-fluorophenylamino)-4-(N-methylphenylamino)-8-fluoroquinazoline

In a procedure analogous to that of Example 41 2-chloro-4-(N-methylphenylamino)-8-fluoroquinazoline and  
20 2-methyl-4-fluoroaniline are reacted together to give the title compound.

Example 50

25 Preparation of 2-(2-methylphenylamino)-4-(N-ethylphenylamino)quinazoline hydrochloride

A. Preparation of 4-(N-ethylphenylamino)-2-chloroquinazoline.

30

Substituting N-ethylaniline for N-methylphenylamine and using corresponding molar proportions of other reagents in Example 26A, gives the title compound.

35



- 47 -

B. Preparation of 2-(2-methylphenylamino)-4-(N-ethylphenylamino)quinazoline hydrochloride.

5 Substituting 4-(N-ethylphenylamino)-2-chloro-quinazoline for 4-(N-methylphenylamino)-2-chloro-quinazoline and using molar proportions of the other reagents in Example 26B gives the title compound.

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Biological Data.(A) H<sup>+</sup>K<sup>+</sup>ATPase Activity.

5 The effects of a single high concentration (100  $\mu$ M)  
of a compound of structure (I) on K-stimulated ATPase  
activity in lyophilised gastric vesicles was determined.  
Preferred compounds of structure (I) were also tested  
over a range of concentrations to determine IC<sub>50</sub> values.

10 (i) Preparation of lyophilised gastric vesicles  
(H/K-ATPase).

Lyophilised gastric vesicles were prepared from pig  
fundic mucosa after the method of Keeling et. al. (Biochem.  
Pharmacol., 34, 2967, 1985).

15

(ii) K<sup>+</sup>-stimulated ATPase activity.

K<sup>+</sup>-stimulated ATPase activity was determined at 37°C  
in the presence of the following : 10 mM Pipes/Tris buffer  
pH 7.0, 2 mM MgSO<sub>4</sub>, 1 mM KCl, 2 mM Na<sub>2</sub>ATP and 3-6  $\mu$ g  
20 protein/ml lyophilised gastric vesicles. After incubation  
for 30 minutes, the inorganic phosphate hydrolysed from ATP  
was determined by the method of Yoda and Hokin (Biochem.  
Biophys. Res. Commun. 40, 880, 1970).

25 Compounds of structure (I) were dissolved in  
dimethylsulphoxide which up to the highest concentration  
used had no effect on K<sup>+</sup>-stimulated ATPase activity.

30 The effect of the highest concentration of each  
compound of structure (I) on the recovery of a standard  
amount of inorganic phosphate was also determined.

(iii) Results.

35 The compounds of the examples had IC<sub>50</sub> values in  
the range of from 0.02 to 30  $\mu$ M.

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B. Rat: Lumen perfused stomach (pentagastrin stimulated gastric acid secretion).

Using a modification of the procedure described by  
 5 Ghosh and Schild (Br. J. Pharmacology, 13, 54, 1958), the  
 compounds of the following Examples were found on i.v.  
 administration at a concentration of  $10\mu\text{mole/kg}$  to cause  
 an inhibition of pentagastrin stimulated gastric acid  
 secretion as indicated in the following Table.

	Compound	Rat G.S.
		% inhibition @ $10\mu\text{mole/kg}$
	1	60
15	2	25
	3	16
	4	37
	5	37
	6	48
20	7	20
	8	17
	11	28
	13	20
	15	31
25	16	31
	18	12
	20	72
	21	37
	22	27
30	24	97
	25	24
	26	79
	27	71
	29	13
35	30	23
	31	8
	32	96

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Example A

A tablet for oral administration is prepared by combining

5

Mg/Tablet

	Compound of structure (I)	100
	lactose	153
10	Starch	33
	crospovidone	12
	microcrystalline cellulose	30
	magnesium stearate	2
		-----
15		330 mg
		-----

into a 9 mm tablet.

Example B

20

An injection for parenteral administration was prepared from the following

		%w:w
25	Compound of Example 20	0.50% (w:v)
	1M citric acid	30% (v:v)
	sodium hydroxide (qs)	to pH 3.2
	water for injection EP	to 100 ml

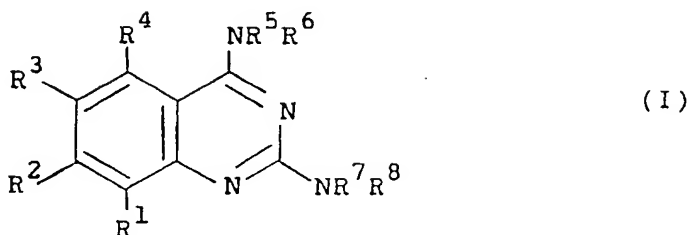
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The compound of Example 20 was dissolved in the citric acid and the pH slowly adjusted to pH 3.2 with the sodium hydroxide solution. The solution was then made up to 100 ml with water, sterilised by filtration and sealed into appropriately sized ampoules and vials.

35

## Claims.

1. A compound of structure (I)



in which

15  $R^1$  to  $R^4$  are the same or different and are each hydrogen,  $C_{1-4}$  alkyl,  $C_{1-4}$  alkoxy, phenyl,  $C_{1-4}$  alkylthio,  $C_{1-4}$  alkanoyl, amino,  $C_{1-6}$  alkylamino, di- $C_{1-4}$  alkylamino, halogen or trifluoromethyl provided that at least two of  $R^1$  to  $R^4$  are hydrogen.

20  $R^5$  and  $R^6$  are the same, or different and are each hydrogen,  $C_{1-4}$  alkyl,  $-(CH_2)_n Ar$  in which n is 0 to 4 and Ar is an optionally substituted phenyl group or  $R^5$  and  $R^6$  together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring; and;

25

$R^7$  and  $R^8$  are the same or different and are each hydrogen,  $C_{1-4}$  alkyl,  $(CH_2)_n Ar^1$  in which n is 0 to 4 and  $Ar^1$  is an optionally substituted phenyl group, or  $R^7$  and  $R^8$  together with the nitrogen atom to which they are attached form a saturated or unsaturated carbocyclic ring;

30

or a pharmaceutically acceptable salt thereof.

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2. A compound according to claim 1 in which  $R^2$  to  $R^4$  are hydrogen and  $R^1$  is hydrogen or  $C_{1-4}$  alkoxy.

3. A compound according to claim 2 in which one of  $R^5$  and  $R^6$  is  $(CH_2)_n Ar$  in which  $n$  is 0 to 4 and  $Ar$  is an optionally substituted phenyl group and the other is  $C_{1-4}$  alkyl.

4. A compound according to claim 3 in which  $n$  is 0.

5. A compound according to claim 4 in which one of  $R^7$  and  $R^8$  is hydrogen and the other is  $-(CH_2)_n Ar^1$  in which  $n$  is 0 to 4 and  $Ar^1$  is an optionally substituted phenyl ring.

6. A compound according to claim 1 which is  
2-amino-8-methoxy-4-(2-methylphenylamino)quinazoline  
2,4-Bis-(N-methylphenylamino)quinazoline  
4-(N-methylphenylamino)-2-(2-methylphenylamino)-8-methoxy-  
quinazoline  
2-(2-methylphenylamino)-4-(N-methylphenylamino)quinazoline  
2-phenylamino-4-(N-methylphenylamino)quinazoline  
2-[(2-methyl-4-fluorophenyl)amino]-4-(N-methylphenylamino)-  
quinazoline  
2-(2-methylphenylamino)-4-phenylaminoquinazoline

or a pharmaceutically acceptable salt thereof,

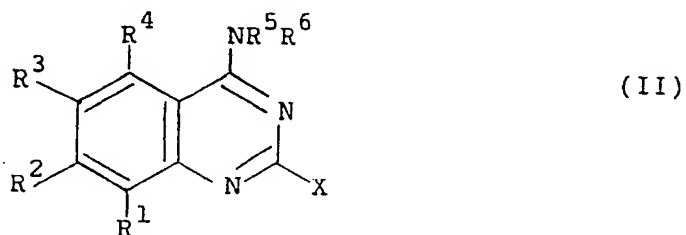
7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 6 and a pharmaceutical carrier.

8. A compound according to any one of claims 1 to 6 for use as a therapeutic agent.

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9. A process for the preparation of a compound according to claim 1 which comprises :

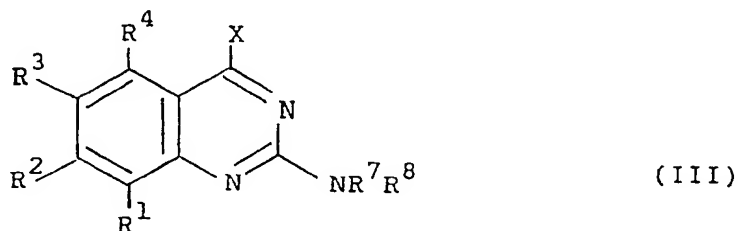
(a) reaction of a compound of structure (II)



in which  $R^1$  to  $R^6$  are as described for structure (I) except that where necessary they are in protected form, and X is a group displaceable by an amine, with an amine of structure  $R^7R^8NH$  in which  $R^7$  and  $R^8$  are as described for structure (I); or

15

(b) reaction of a compound of structure (III)



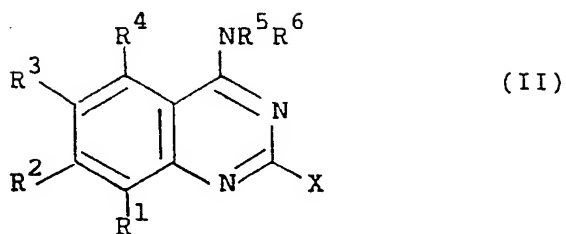
in which  $R^1$  to  $R^4$  and  $R^7$  and  $R^8$  are as described for structure (I) and X is a group displaceable by an amine, with an amine of structure  $R^5R^6NH$  in which  $R^5$  and  $R^6$  are as described for structure (I); and optionally thereafter,

30

- ° removing any protecting groups;
  - ° forming a pharmaceutically acceptable salt.
- 35

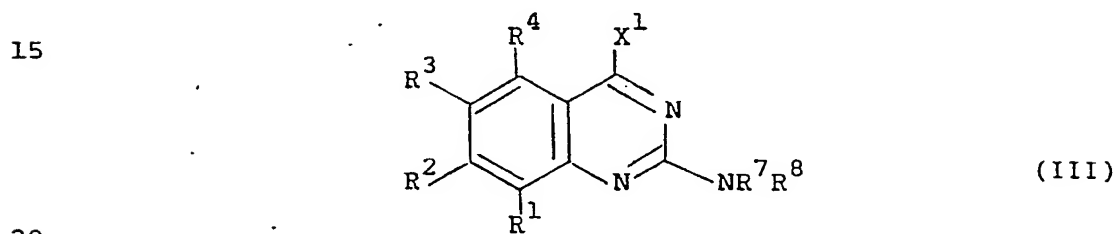
- 54 -

10. A compound of structure (II)



10 in which  $R^1$  to  $R^6$  are as described for structure (I) in claim 1 and X is a group displaceable by an amine.

11. A compound of structure (III)



in which  $R^1$  to  $R^4$  and  $R^7$  and  $R^8$  are as described for structure (I) in claim 1 and X is a group displaceable by an amine.

25

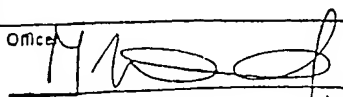
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# INTERNATIONAL SEARCH REPORT

International Application No. **PCT/EP 88/01127**

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>1</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC <sup>4</sup> : C 07 D 239/95; A 61 K 31/505; C 07 D 401/04		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System <sup>1</sup>	Classification Symbols	
IPC <sup>4</sup>	C 07 D 239/00	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT <sup>9</sup></b>		
Category <sup>9</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	DE, C, 958197 (S. SKRAUP) 14 February 1957 see pages 1,2 --	1
X	GB, A, 806772 (WELLCOME) 31 December 1958 see pages 1,2 --	1,7,8
X	FR, A, 1310457 (WELLCOME) 22 October 1962 see pages 1-3 --	1,7,8
X	US, A, 3635979 (H.-J. HESS) 18 January 1972 see columns 1-26 --	1,7-11
X	CH, A, 457460 (PARKE, DAVIS) 15 August 1968 see columns 1-6 --	1
X	US, A, 4098788 (R.R. CRENSHAW) 4 July 1978 see columns 6-10	10
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"Δ" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
3rd April 1989	03.05.89	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	M. VAN MOL 	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	US, A, 3956495 (W.B. LACEFIELD) 11 May 1976 see columns 1-3,7-18 --	1,7,8,10
X	EP, A, 0028473 (PFIZER) 13 May 1981 see pages 5,11-15,42,43,68-78; claims --	1,7-11
X	GB, A, 1390014 (N.V. KONINKLIJKE PHARMACEUTISCHE FABRIEKEN V/H BROCADES-STHEEMAN & PHARMACIA) 9 April 1975 see pages 1,2,4-9 ----- -----	1,7,8

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 8901127  
SA 25841

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/04/89. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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		GB-A- 1390015	09-04-75

